Medical Progress

Cardiovascular Effects of Alcohol

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The effects of alcohol on the heart include modification of the risk of coronary artery disease, the development of alcoholic cardiomyopathy, exacerbation of conduction disorders, atrial and ventricular dysrhythmias, and an increased risk of hypertension, hemorrhagic stroke, infectious endocarditis, and fetal heart abnormalities.

(Davidson DM: Cardiovascular effects of alcohol. West J Med 1989 Oct; 151:430-439)

Although the harmful effects of alcohol on the heart were first reported more than a century ago, only in the past 30 years have investigators clarified the effects of the consumption of alcohol on the cardiovascular system through studies of animals and humans.[1,2]

Alcohol can exacerbate hypertension and affect levels of other indicators of risk for coronary artery disease (CAD) and stroke. These changes place heavy drinkers at a greater risk for a myocardial infarction, sudden cardiac death, and stroke. Considerable controversy persists, however, regarding the possible advantages of light alcohol consumption, usually defined as less than 1 oz (two drinks) per day.

In this essay I review recent evidence regarding the harmful and potentially beneficial effects of alcohol use on the human heart. The initial and long-term responses of the myocardium to alcohol use will be considered first, along with its treatment and possible reversibility. I will then describe the effects on cardiac conduction and rhythm, noting the increased risk of sudden cardiac death in heavy drinkers. I discuss the effects of alcohol intake on hypertension and other risk indicators for coronary artery disease and summarize the epidemiologic evidence linking alcohol use to myocardial infarction and stroke. Finally, I describe the relationships of alcohol use to infectious endocarditis and fetal heart abnormalities.

Investigational Issues

Studies of the alcohol-heart relationship are methodologically difficult for many reasons. One major issue involves comparisons of nondrinkers and drinkers; the two groups are rarely formed randomly. Self-reporting of current and past drinking habits is usually obtained from those who choose to participate in a study, leading to certain problems.

Included among nondrinkers (current abstainers) are both ex-drinkers and persons who never drink; the former may have cardiac problems or altered cardiovascular risk factors due to their previous excessive consumption. In a prospective study of 7,735 British men, investigators found that long-term ex-drinkers had many characteristics that increase their cardiovascular risk. They were more likely to be unmarried and to work in manual occupations. Their prevalence of cigarette smoking, hypertension, and obesity was much higher than that of persons who never drink but was similar to that of moderate and heavy drinkers. Of all groups, ex-drinkers had the highest prevalence of angina and definite myocardial infarction by electrocardiogram, and they had a rate of recall of ischemic heart disease diagnosed by their physician that was twice that of drinkers.[3] Lifelong abstainers have less psychosocial dysfunction than ex-drinkers, are more likely to be religious, have less education, live in rural areas, and have lower incomes.[4,5] Thus, ex-drinkers clearly should be separated from the never-drinking group.

Another methodologic obstacle is defining the drinking population. In most population studies, those who do not participate have different characteristics from those who do. For example, in establishing the Göteborg (Sweden) Primary Prevention Trial study population, 25% of 10,000 invited men declined to be enrolled. After a 12-year follow-up, investigators found that nonparticipants had twice the mortality as participants; most of the excess deaths were sudden. Nonparticipants were more often registered with the Board of Social Welfare for social problems and alcohol abuse.[6]

Those who do participate may not report alcohol intake accurately,[7] although one study of patients and spouses showed agreement within one category of consumption in 90% of cases.[8] If reporting is accurate, then the decision of how to aggregate the data obtained must be made. Are seven drinks every Saturday night equivalent to one drink daily each week in terms of health effects? Many investigators express alcohol consumption in terms of ounces of pure ethanol consumed per day or week.[9] One drink can be defined as a 12-oz beer with 3% to 5% ethanol, a 5-oz glass of wine (12%), or a 1.5-oz shot of spirits (80 proof = 40%). Each contains 0.6 oz (17 ml = 13.6 grams) of ethanol.

Myocardial Dysfunction

Pathophysiology

Animal models are traditionally used to elucidate the pathophysiology of human diseases, but this is difficult with alcoholic cardiomyopathy. Myocardial changes consistent with subclinical human heart disease have been produced, but impairment leading to congestive heart failure has not been replicated.[1]

Several mechanisms have been postulated by which eth-

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Supported in part by the National Heart, Lung, and Blood Institute Preventive Cardiology Academic Award, HL 01243.

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ABBREVIATIONS USED IN TEXT

BP = blood pressure
CAD = coronary artery disease
HDL = high-density lipoprotein
LDL = low-density lipoprotein
LV = left ventricular
VLDL = very-low-density lipoprotein

anol damages the heart. These include a direct toxic effect, action by ethanol metabolites, and a neurohumoral mechanism.[1] Mitochondrial changes—enlargement, decreased respiration, release of enzymes, and reduced ion transport—have been observed after long-term exposure to ethanol, associated with membrane damage, increased calcium flux, impaired adenosine triphosphatase activity, decreased fatty acid oxidation, and depressed adenosine triphosphate levels.[10-12] Persistent impairment of mitochondrial function may be due to the formation of fatty acid ethyl esters, which bind to mitochondria. When the esters are hydrolyzed, free fatty acids are released, leading to the uncoupling of oxidative phosphorylation.[13]

Some investigators think that acetaldehyde mediates this damage.[14] The effects of ethanol's major metabolites, acetaldehyde and acetate, have also been investigated in the peripheral and cerebrovascular circulations. The vasoconstrictor and vasodilator effects of these metabolites may be related to calcium movement across vascular smooth muscle cell membranes.[15]

Interstitial edema and focal areas of necrosis are noted histologically in myocardial tissue. Coronary arteries are usually patent, but it should be remembered that studies often exclude subjects with symptomatic coronary artery disease.

It is difficult clinically to distinguish alcohol-induced myocardial damage from other types of dilated cardiomyopathy,[2] so often the diagnosis must be made by excluding other causes in a person with a history of heavy alcohol intake.

Epidemiology

A disproportionate number of cases of alcoholic cardiomyopathy occur in men, even when sex differences in alcohol intake are considered. Similarly, preclinical cardiomyopathy is detected in men more frequently than in women.[16] Precise prevalence and incidence figures have yet to be determined, largely because of the methodologic difficulties discussed previously. The typical symptomatic patient is a middle-aged man who has been a heavy drinker for at least ten years, deriving 30% to 50% of his calories from alcohol. It is suspected, however, that most persons with alcoholism have subclinical heart disease. An autopsy study in Detroit of alcoholic persons with no premortem clinical signs of cardiomyopathy revealed an increased heart size in many cases; in those hearts without cardiomegaly, gross and microscopic pathologic changes consistent with cardiomyopathy were noted.[17]

In several cities, the addition of cobalt to the beer-brewing process resulted in a toxic cardiomyopathy distinct from the effect of alcohol on the myocardium.

Nutrition

For some years, the pathogenesis of alcoholic cardiomyopathy was attributed to nutritional deficiencies such as beriberi because both conditions may result in congestive heart failure. In contrast to alcoholic cardiomyopathy, however, beriberi is characterized by a high cardiac output due to peripheral arteriolar dilation. Chest pain is nonspecific, and the electrocardiogram may be normal.[18] Thiamine deficiency in this condition may result from inadequate dietary intake or through increased metabolism. The latter is particularly the case in beer and wine drinkers, perhaps because the higher carbohydrate content of those beverages can increase thiamine requirements. Fortunately, cardiac sequelae can be reversed with the administration of thiamine.[19]

Other nutritional deficiencies may arise if calories from alcohol replace those from other sources. This occurs more often in alcoholic persons than in mild to moderate drinkers. Alcohol interferes with food absorption and may alter appetite and satiety.[20]

Compared with nondrinkers, Scottish men with moderate alcohol intake had lower intakes of total, saturated, and monounsaturated fats. Persons drinking one drink per day or less had a higher intake of fiber and polyunsaturated fatty acids.[21] These differences may play some role in the relationship of alcohol intake to the coronary artery disease incidence, as will be described.

Initial Myocardial Effects

Readers will recall that the cardiac output is the product of heart rate and stroke volume and that the product of the cardiac output and total peripheral resistance equals the mean arterial blood pressure. The stroke volume often reflects the myocardial contractile state, but the dynamic relationships among these variables require consideration of each during an intervention.

The initial effects of alcohol ingestion are highly dose dependent. After only 2 oz of whisky, the cardiac output and stroke volume increased in normal subjects, while the same measures decreased in cardiac patients.[22] The enhanced hemodynamics in normal subjects reflect increased circulating catecholamines, which in turn can increase contractility. When this sympathetic nervous system response is blocked pharmacologically, the myocardial depressant effect of acute ethanol ingestion becomes clear.[23]

At higher doses, peripheral vasodilation is noted, along with a decrease in blood pressure and compensatory increases in heart rate.[24] During isometric[25] or dynamic exercise,[26] these hemodynamic changes compensate for the myocardial depressant effect of alcohol. Alcohol may potentiate the effects of pharmacologic vasodilators such as nitroglycerin.[27]

In patients with moderate to severe congestive heart failure—New York Heart Association classification III and IV—no decrease in myocardial performance was noted after 0.9 grams per kg body weight of vodka was consumed, reflecting the vasodilatory properties of alcohol.[28] When patients with transmural myocardial infarction were given 2 oz whiskey seven to ten days after their infarction, however, the stroke volume and cardiac output both decreased due to a decline in left ventricular contractility in the peri-infarct zones.[29]

Moreyra and co-workers reported three cases of acute myocardial infarction in young persons after an episode of heavy alcohol intake. All had normal coronary arteries, suggesting that thromboembolism or coronary artery spasm might have been involved.[30]

Long-term Myocardial Effects

Long-term damage to the myocardium in drinkers is related to both the frequency and duration of excess alcohol consumption. Earlier studies examined the cardiothoracic ratio on chest roentgenograms and noted sinus tachycardia and T-wave abnormalities on electrocardiograms, but both findings were nonspecific.[31] Several authors have described pronounced T-wave abnormalities in patients with alcoholic cardiomyopathy who had hypomagnesemia.[32]

Using systolic time intervals derived from phonocardiography and electrocardiography, investigators noted significant differences in the mean values of the pre-ejection period and left ventricular ejection time between normal subjects and asymptomatic alcoholic persons, but considerable overlap remained between values in the two groups.[33] Newer noninvasive cardiovascular diagnostic techniques, however, have successfully differentiated asymptomatic drinkers with early myocardial changes from normal healthy persons.

Echocardiographic studies in persons recovering from alcoholism have been carried out during the first week,[31] at least two weeks after,[33] and an average of a month after[34] their last alcoholic drink. Using values greater than two standard deviations above the mean as abnormally high, Askanas and colleagues noted that half of their asymptomatic alcoholic subjects (three to six days after last drink) had abnormally increased thickness of the intraventricular septum and posterior left ventricular (LV) wall, leading to an abnormally high estimate of LV mass. Echocardiographic indices of contractility (percent fractional shortening, ejection fraction, and circumferential fiber shortening) and chamber diameters (left atrial and left ventricular at end-diastole and end-systole) were much less specific.[31]

Mathews and associates studied 22 asymptomatic and 11 symptomatic alcoholic persons at least 14 days after their last drink. They also found about half of their asymptomatic subjects had abnormally high septal and free wall LV thicknesses and LV mass. Among their symptomatic patients, all 11 had abnormally high left ventricular dimensions and 10 of the 11 had elevated left ventricular mass. In the latter group, however, septal and wall thicknesses were only modestly increased, compatible with a dilated cardiomyopathy without hypertrophic thickening of the myocardium.[33]

Kino and co-workers examined 145 alcoholic men in Japan, noting increased echocardiographic estimates of left ventricular mass with consumption exceeding 125 ml of ethanol daily for ten years or more.[34] Their studies were done over a wide range of abstention times (minimum one week, average one month), however, raising the issue of a possible regression of LV changes after the cessation of alcohol intake.[34] In fact, an improvement in myocardial function after several months of abstention has been found using echocardiography[35,36] and radionuclide ventriculography.[37]

Cardiac catheterization can document reduced cardiac output and elevated filling pressures. Contrast ventriculography often reveals an enlarged, hypocontractile left ventricle, but a tendency for a preservation of contractility in the basal portions has been noted.[2]

Clinical Course and Treatment

Several authors described the natural history of alcoholic cardiomyopathy in the decades before the availability of vasodilators and other pharmacologic agents for the treatment of dilated cardiomyopathies. Tulane University (New Orleans) investigators used prolonged bed rest (6 to 671 days) but concluded that the ultimate prognosis was poor because of their subjects' unwillingness to accept the immobility and to resist the temptation to resume drinking.[38] Demakis and associates observed a strong relationship between abstaining and an improved clinical state in patients without prolonged bed rest. Among abstaining patients, 61% showed clinical improvement, compared with only 10% of heavy drinkers.[39]

The symptoms and signs of alcoholic cardiomyopathy are consistent with the extent of congestive heart failure. Frequently reported are orthopnea, paroxysmal nocturnal dyspnea, and dyspnea on exertion. Physical signs include a sinus tachycardia, third and fourth heart sounds, rales, hepatomegaly, and peripheral edema. The results of cardiac catheterization studies in such patients confirm increased left ventricular end-diastolic (filling) pressures, leading to increased pulmonary vascular pressures and the symptoms of congestive heart failure.

The most important goal of treatment is to help a patient remain abstinent, with the hope of reversing the myocardial changes. Most quantitative studies suggest that this process may require as long as a year or more,[37,40,41] although cases of quicker recovery have been reported.[35]

In general, the pharmacologic therapy for alcohol-induced myocardial dysfunction follows current recommendations for dilated cardiomyopathy of any cause.[42,43] In the presence of a dilated left ventricle, administering vasodilators and digoxin is indicated, as well as the use of diuretics when an increased LV filling pressure has resulted in symptoms of congestion. Angiotensin-converting enzyme inhibitors are also useful; when combined with the use of diuretics, they minimize the probability of hypokalemia.[42] Alderman and Coltart point out that digoxin should be used cautiously because of an increased susceptibility to toxicity in patients with advanced heart failure and because hypokalemia is more common in heavy drinkers. They also recommend caution in anticoagulating such patients; the possible benefit of such treatment to reduce the likelihood of emboli may be counterbalanced by hepatic dysfunction and less reliability of such persons in self-administering medication.[2]

Because left ventricular failure is frequently accompanied by dysrhythmias and conduction disorders, these will now be considered in the context of alcoholic cardiomyopathy.

Conduction Disorders and Dysrhythmias

Studies in animals and humans have documented various conduction disorders in chronic alcoholism, including a prolonged PR interval, Mobitz I and II block, right and left bundle branch block, and complete heart block.[44-46] In one study, the ingestion of 60 ml of whiskey prolonged atrial conduction and decreased ventricular refractory periods in nonalcoholic cardiac patients.[22]

More common are atrial and ventricular dysrhythmias, the prevalence of which depends on the frequency and duration of alcohol intake and the underlying state of the myocardium.

Atrial Dysrhythmias

Various atrial dysrhythmias have been noted after spree or holiday drinking, including premature atrial contractions, atrial tachycardia, atrial flutter, and atrial fibrillation.[45]

Suspecting that alcohol use was part of the cause of new cases of atrial fibrillation, Lowenstein and co-workers reviewed the records of 40 such consecutive patients in their hospital. They found that alcohol intake had caused or contributed to the dysrhythmia in 35% of all cases and in 63% of persons younger than 65 years.[47] Case-control studies of this phenomenon have documented an association with alcohol use in 15% to 63% of cases of paroxysmal atrial fibrillation.[48,49] Infrequent drinkers may also have atrial fibrillation after a drinking binge.[50] Electrophysiologists have induced atrial fibrillation in susceptible patients with as little as 60 ml of whiskey.[51] In one case, atrial fibrillation recurred in a man who used large amounts of alcohol-rich breath spray.[52] Investigators have suggested the involvement of several mechanisms, including increased levels of circulating catecholamines and altered myocardial refractory periods and conduction times.[51,53,54]

The question may next be asked if habitual alcohol users are more susceptible to these conditions. One group found no differences in the prevalence of atrial dysrhythmias between normal subjects and heavy drinkers with normal myocardial function.[55] In another study, information about heavy drinkers with presumed greater myocardial involvement was obtained when 1,322 persons reporting consuming six or more drinks per day were compared with 2,644 drinkers who reported drinking at least monthly but less than daily. The relative risk in the heavier drinkers was at least doubled for atrial fibrillation, atrial flutter, supraventricular tachycardia, and atrial premature complexes.[56]

Ventricular Dysrhythmias

Increased ventricular ectopic activity, including ventricular tachycardia, has been documented after intensified ingestion of alcohol in persons with[53] and without[57,58] apparent heart disease. In addition to catecholamine effects, possible etiologic factors include heterogeneous refractory periods throughout the myocardium and prolonged His-Purkinje intervals.[53]

Ventricular dysrhythmias may also occur in the alcohol withdrawal period, although certainty about their cause is complicated by the presence of coronary artery disease,[59] electrolyte and mineral disorders,[60] delirium tremens,[61] and medical treatment.[62,63]

Sudden Cardiac Death

Although ventricular dysrhythmias are more common—and more easily induced—in heavy drinkers, evidence for a notably increased risk of primary cardiac arrest is largely indirect. This arises from the high prevalence of coronary artery disease in persons dying suddenly, varying definitions of "sudden," and inconsistencies in coding the causes of death in the absence of an autopsy.

In a Soviet series of 50 autopsies, 30 persons had died suddenly. All had had chronic alcoholism, and 17 of the 30 had substantial blood alcohol levels at the time of their death. Compared with control subjects who died of lethal alcohol intoxication, those dying suddenly had greater degrees of myocardial hypertrophy, fibrosis, and necrosis.[64]

Registration with the Swedish Temperance Board was associated with increased risks of sudden cardiac death in 50-year-old men observed prospectively for ten years.[65] Similarly, men who chose not to participate in the Göteborg Primary Prevention Trial were more often registered for alcohol problems and had a higher incidence of coronary artery disease deaths. The excess CAD mortality in nonparticipants was largely accounted for by sudden cardiac deaths.[6,66,67] In a longitudinal study of 50-year-old men in Uppsala, half of all men dying suddenly were registered at the Temperance Board.[68,69]

In a five-year Finnish study of 4,532 men aged 40 to 64 years, investigators found that the incidence of sudden death was much lower in abstainers, regardless of the presence of coronary artery disease. This reduced risk was more pronounced in the oldest age group and was true for both smokers and nonsmokers.[70]

The Framingham study reported an increased risk of "sudden death not preceded by definite clinical evidence" of coronary heart disease in persons drinking more than 90 oz per month.[71] A case-control study of sudden unexpected death in women in Rochester, Minnesota, showed that 40% of cases had a diagnosis of alcoholism compared with 6.8% of patients with myocardial infarction and 3.3% of controls.[72]

In a New Zealand study in which spouses of persons who had died suddenly were interviewed, alcohol intake was positively associated with the terminal event, although the investigators noted that persons dying within an hour of symptoms had lower weekly alcohol consumption than those dying later during the first day.[73]

Not all studies, however, have found a positive relationship between sudden death and alcohol intake. In the Kaiser-Permanente experience, "instantaneous" sudden cardiac death was no more likely in current drinkers than in those who were reported to have consumed no alcohol in the past year.[74]

Risk Indicators for Coronary Artery Disease and Stroke

Before considering the overall impact of alcohol on CAD and stroke incidence, the effects on individual risk factors for those diseases will be considered.

Blood Pressure

In 1915 Lian described the association of hypertension with alcohol intake, noting a higher prevalence in French army officers with the greatest alcohol consumption.[75] During the next several decades, however, the association was largely ignored.[76] In the past ten years, numerous studies have been conducted worldwide on alcohol-related hypertension.[77] The topic is complex, subject to all of the methodologic concerns mentioned earlier as well as a complex interaction with electrolytes and minerals[78] not discussed here.

Initial effects. In normotensive subjects who usually drank little or no alcohol, blood pressures rose slightly after drinking 1 gram per kg body weight for five days. The same was true in hypertensive light drinkers. In contrast, hypertensive subjects who had been consuming their usual moderate amounts of alcohol had a greater response to an alcohol challenge.[79]

A British study was done of male and female alcoholic patients with a mean age of 44 years. Each had a daily intake of more than 80 grams (mean, 196 grams). The average duration of heavy drinking was 15.8 years (range 2 to 50). The blood pressure (BP) was taken before cessation, during detoxification, and after two months of abstinence. The initial blood pressure exceeded 140/90 mm of mercury in more

than half of subjects. A significant linear positive correlation was noted between the initial blood pressure and the mean daily intake during the three months preceding admission. Withdrawal symptoms were most severe in those with the highest initial pressures. In most subjects, the BP fell to normal—mean, 137/87 to 122/77 mm of mercury—after detoxification and remained low—122/75 mm of mercury—in subjects who remained abstinent for a year or more. It rose again, however—128/81 to 144/89 mm of mercury—in those who resumed drinking alcohol.[80]

Evidence for the acute effects of alcohol on the blood pressure also comes from studies during withdrawal. Reducing alcohol intake in hypertensive men from six to eight drinks per day to none resulted in a decrease in systolic and diastolic pressure of 13 and 5 mm of mercury, respectively, over a three- to four-day period.[81] In another study, patients continued their usual antihypertensive medications during six weeks of usual drinking and six weeks of consuming only a low-alcohol beer. The mean alcohol consumption dropped from 452 ml per week to 64 ml per week. During the last two weeks of the low-alcohol period, the systolic and diastolic pressures had dropped 5 and 3 mm of mercury, respectively, from the usual drinking period.[82] In normotensive men, a decrease from three drinks per day to three drinks per week decreased the systolic BP by 4 mm of mercury but did not significantly change the diastolic pressure over a period of six weeks.[83]

Using a randomized, open crossover design, Howes studied normotensive persons previously consuming 10 to 40 grams of alcohol a day. Compared with four days of consuming 80 grams per day, subjects had drops of 8 and 6 mm of mercury in the systolic and diastolic BPs, respectively, after four days of abstinence.[84]

Long-term effects. Some have suggested that hypertension is at least twice as common in persons with alcoholism[85] and that alcohol use may be the most common cause of secondary hypertension.

Klatsky and co-workers studied blood pressure and usual drinking habits in 83,947 men and women who were members of Kaiser Permanente.[86] Participants were asked to report their alcohol consumption in one of three categories (drinks per day): two or less, three to five, and six or more. Men in the lowest category had BPs similar to control subjects, but women in the lowest category had BPs lower than controls. In both men and women, those reporting consuming three or more drinks daily had higher systolic and diastolic pressures and a higher prevalence of BPs of 160/95 mm of mercury or higher. These associations were independent of age, sex, race, smoking, caffeine use, former "heavy drinking," educational attainment, and adiposity. Compared with nondrinkers, persons consuming six or more drinks per day had a prevalence of hypertension that was doubled in whites and 1.5 times in blacks.[86]

The investigators also reviewed early Framingham data, noting that men who consumed 100 oz per month or more had mean systolic blood pressures 7 mm of mercury higher than lighter drinkers; hypertension—higher than 160/95 mm of mercury—was twice as prevalent in those who drank 60 oz or more per month compared with those drinking 10 to 29 oz per month.

In the Lipid Research Clinics Prevalence Study, systolic and diastolic pressures were both linearly related to alcohol intake. An analysis of regression coefficients suggested that a daily consumption of 30 ml would increase the systolic BP by 2 to 6 mm of mercury. Investigators also noted that an elevated BP was more strongly associated with past 24-hour consumption than with intake during the preceding six days.[87]

In a study of volunteer Australian men, a quarter of whom drank more than 50 ml a day, investigators found a linear increase of blood pressures with a mean daily alcohol consumption at increments of 1-mm-of-mercury systolic BP for each drink a day. The mean systolic BP was 5 mm of mercury higher in heavy drinkers than in nondrinkers. They also noted that heavy and moderate drinkers (53% of the study population) were both four times more likely to have a systolic BP of 140 mm of mercury or higher and three times more likely to have a diastolic BP of 90 mm of mercury or higher. Previous drinkers had blood pressures similar to those who never drank.[88] These relationships were noted for all levels of obesity, which is another powerful predictor of hypertension.[89]

The Stanford (California) Five City Project is a community health education study designed to reduce the prevalence of cardiovascular risk factors and the incidence of cardiovascular disease in entire communities. Subjects included 883 men and 959 women aged 20 to 74 years not taking blood pressure medications. The association of blood pressure and dietary alcohol was linear in all men and in women older than 49, particularly in those not taking replacement estrogens. Systolic BP effects were more pronounced than those of diastolic BP.[90]

Approximately half of reported studies have found a J-shaped relationship of alcohol use and blood pressure.[77] An analysis of the Tecumseh, Michigan, study data showed that the lowest blood pressures were associated with 1.5 drinks per week in men and about four drinks per week in women.[91] In at least one study, however, lighter drinkers were younger and leaner,[92] suggesting that the other health habits of light drinkers might also influence the blood pressure. But in other studies, the J-shaped curve was independent of those physiologic variables.[86,91]

Studies also differ in their "threshold" values—levels of alcohol consumption above which the blood pressure invariably rises. The Lipid Research Clinics study estimated this value to be 20 to 30 ml a day. In the Kaiser-Permanente study, this level was 90 ml a day[86]; a later investigation found a threshold in women only.[93] Other investigators found no threshold in either sex.[80,88]

Several investigators have found that alcohol effects on the blood pressure are greater in older persons,[87,90,93] but the Michigan investigators noted greater effects on the systolic blood pressure in persons aged 18 to 39.[94]

It is unclear whether the type of alcoholic beverage consumed is important. The later Kaiser study noted greater pressor effects from beer and liquor consumption than from wine, as did the Lipid Research Clinics study.[93,95] In an Italian study, however, wine drinkers had a higher prevalence of hypertension than nondrinkers of both sexes.[96]

Incidence. Investigators of the prospective Chicago People's Gas and Western Electric studies found that heavy alcohol users had greater increases in blood pressure than did nondrinkers.[97] Similar findings were obtained in the Zutphen (Netherlands) Study.[98] The Framingham Offspring Study also found a positive relation of blood pressure to alcohol intake in 4,294 men and women observed for eight years.[89]

Etiology. In a study of monozygotic and dizygotic twin pairs who were discordant for alcohol use, an association of blood pressure and alcohol use that was independent of genetic factors was noted.[99] Evidence for a direct pressor effect of alcohol is now fairly well established[83]; this may result from interference with central inhibitor pathways or through modified calcium transport.[88] Psychosocial stress is another possible contributor because it may raise both the level of alcohol consumption and the blood pressure.[100]

Adherence. Investigators have noted that persistent drinkers do not achieve as great an antihypertensive effect from drugs as do nondrinkers on the same pharmacologic regimen.[80] In a trial during which antihypertensive medications were withdrawn, persistent drinkers were much more likely to require the resumption of medication.[101] Others have noted that the cessation of alcohol drinking is often accompanied by a better adherence to a medication regimen.[102,103]

It is difficult to estimate the percentage of persons who have hypertension due solely to alcohol consumption. More important, however, is the public health effect of reducing moderate to high alcohol consumption in all hypertensive drinkers. While the blood pressure may fall after the cessation of drinking, it is not certain if alcohol-induced myocardial hypertrophy will be reversible.

Hemostasis

Alcohol ingestion may influence heart disease through hemostatic mechanisms.[104] In studies of healthy volunteers, Hillbom and co-workers noted an activation of the coagulation cascade, including decreased fibrinolytic activity, increased factor VII coagulant activity, and shortened bleeding times after excessive alcohol intake,[105] as well as increased platelet reactivity to adenosine diphosphate and associated formation of thromboxane B_2.[106]

In addition to coagulation abnormalities due to cirrhosis, habitual drinkers are at further risk. Thrombocytopenia is frequently found in heavy drinkers,[107] along with decreased platelet aggregability after acute ingestion[107,108] and during long-term use.[109-111] Investigators have noted decreased platelet counts in subjects during alcohol detoxification,[112] followed by rebound thrombocytosis.[112,113] Platelet hyperaggregability, unrelated to smoking or drug treatment, also occurs during withdrawal.[114,115]

Meade and associates have documented lower fibrinogen levels and increased thrombolysis with increased alcohol consumption.[109] Pikaar and colleagues provided four different daily doses of alcohol to normal (nonalcoholic) subjects during a five-week study. They noted a linear increase in plasminogen levels with increased alcohol intake, along with greatly reduced levels of tissue-type plasminogen activator. Collagen-induced platelet aggregation was reduced during alcohol consumption, while no change was observed in platelet aggregation induced by adenosine diphosphate, platelet secretion, or hematologic values.[111] In two other studies, bleeding time was prolonged within an hour after alcohol ingestion,[107,108] but others have found no effect on bleeding time.[115]

Lipids

The role of lipids and lipoproteins in coronary artery disease risk has been well established, but their influence on stroke risk is less well studied.[115] In most studies, total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides are measured directly. Using the Friedewald formula[116] and estimating the levels of very-low-density lipoprotein (VLDL) cholesterol to be a fifth of those of triglycerides, low-density lipoprotein (LDL) cholesterol is calculated as follows,

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - \text{triglycerides}/5.$$

Concentrations have been expressed in milligrams per deciliter in the United States, and efforts are now being made to have them expressed in millimoles per liter, as they are elsewhere.

Most epidemiologic studies show a direct correlation between CAD risk and total cholesterol, LDL-cholesterol, and triglyceride levels. Debate continues regarding the independent contribution of the triglyceride level to CAD risk. In a recent study, HDL cholesterol appeared to account for most of the triglyceride-CAD association.[117]

High-density-lipoprotein cholesterol has two main subfractions, HDL_2 and HDL_3 cholesterol. The former has been inversely associated with the risk of coronary disease in most studies, but only recently has HDL_3 cholesterol been found to be an important predictor of a reduced CAD risk.[118,119] Apolipoproteins may be better indicators of the CAD risk; apolipoprotein A-I is inversely associated with coronary artery disease, and apolipoprotein B is directly correlated.

The influence of alcohol on lipid, lipoprotein, and apolipoprotein levels depends in part on drinking patterns and accompanying liver damage.[120] Triglyceride levels are positively related to alcohol intake, even after adjusting for obesity and serum cholesterol level,[121,122] probably due to increased secretion of VLDL from the liver. The total cholesterol effects of alcohol often represent the relative effects of LDL cholesterol (no effect or slightly decreased levels) and HDL cholesterol (usually an increase). Dietary factors play an important role in LDL levels, making analysis of studies in alcoholic patients difficult if accurate nutritional information cannot be obtained. Some have suggested that the apparent protective effect of alcohol against coronary artery disease may be applicable only in those consuming high amounts of dietary cholesterol or saturated fat.[5]

Much attention in recent years has focused on alcohol and HDL cholesterol. The excitement engendered by reports of both lower coronary artery disease rates in persons with high HDL-cholesterol levels and higher HDL-cholesterol levels with increased alcohol consumption was dampened somewhat after the results of fractional analyses of HDL cholesterol were reported. In most studies of nonalcoholic persons, the alcohol-induced rise occurs in the HDL_3-cholesterol subfraction, which, until recently, was not thought to exert a CAD protective effect.[5,123] In a study of 234 alcoholic persons, Dai and co-workers noted an increase in both HDL-cholesterol subfractions with increasing alcohol intake until 450 ml of daily consumption, after which both total HDL- and HDL_2-cholesterol levels decreased. Alcoholic subjects with liver disease had higher levels, and HDL-cholesterol levels and those of both subfractions decreased considerably during a month of abstinence,[124] an observation shared by others.[123,125,126] Possible pathways relating HDL cholesterol and alcohol include mediation through sex hormones, as reflected in increased HDL-cholesterol levels in women and decreased testosterone levels in alcoholic men, increased degradation of VLDL, and mediation through microsomal

enzyme induction in the liver.[124] In one study, cessation after long-term drinking resulted in decreases in HDL-cholesterol and lipoprotein lipase activity of approximately 40%.[127]

Experimental studies of moderate alcohol consumption on apolipoprotein levels generally show a relationship of intake and increased apolipoprotein A-I levels.[128,129] This effect can be seen in alcohol doses as small as one drink per day.[130] In studies of alcoholism, Avogaro and colleagues described decreased apolipoprotein A-I levels in patients with liver disease,[131] and two other investigations noted decreased A-I levels after alcohol withdrawal.[127,132]

Thus, it appears that mild to moderate alcohol consumption is associated with more favorable lipid and lipoprotein profiles and a reduced risk of coronary artery disease, although the mechanisms underlying these associations remain unclear. Heavier consumption leading to alcohol abuse and coexisting liver impairment is associated with adverse lipid and lipoprotein profiles and increased coronary artery disease risk.[133]

Smoking

Because the heaviest drinkers are often heavy smokers, the possibility that the alcohol-coronary artery disease association is due solely to tobacco consumption must be eliminated. While the earliest studies did not control for smoking, more recent trials have done so, establishing an independent role for heavy alcohol use in patients with coronary disease.[67] A study of twins confirmed an incidence of coronary artery disease and stroke deaths in heavy drinkers, regardless of smoking status. The Multifactor Primary Prevention Trial in Göteborg found the CAD risk to be highest in those who smoked and drank—the relative risk being 4.2 compared with that in nonsmoking nondrinkers.[67]

Benowitz and co-workers studied the cardiovascular responses of normal subjects to the oral ingestion of alcohol and the intravenous administration of nicotine. Ethanol administration raised the heart rate, systolic blood pressure, and their product, and nicotine had an additive effect on the heart rate and the rate-pressure product. The vasoconstricting effect of nicotine was antagonized by alcohol. They concluded that the combined effects could contribute to dysrhythmias in patients with coronary artery disease.[134]

Coronary Artery Disease

Myocardial ischemia can result from any or a combination of the following processes in the coronary arteries: atherosclerosis, vasospasm, thrombosis, and emboli. The effects of alcohol on these processes, as well as the multiple indicators of CAD risk, have been discussed earlier. In the aggregate, it appears that the alcohol-CAD relationship is dose-dependent. In heavy drinkers—such as drinking six or more drinks per day, or being registered with temperance boards—coronary artery disease mortality (particularly sudden death) is increased. At mild to moderate levels of intake, however, evidence suggests no elevation in the CAD risk.

Heavy Drinkers

Several studies in the United States have documented the increased risk of consuming six or more drinks a day. In Chicago Dyer and associates noted that this increased risk persisted even beyond the first ten years of surveillance.[135] British men drinking more than five drinks per day had higher coronary artery disease incidence rates than lighter drinkers.[136] Investigators in a Massachusetts study showed an increased risk from consuming more than 34 grams per day.[137] Similar results were obtained in a New Zealand study, particularly for sudden cardiac death.[73] In a Swedish study, persons not registered with the temperance board had the lowest coronary disease rates. In comparison, the incidence in all those registered was doubled; for the heaviest drinkers, rates were three times higher.[66]

Nondrinkers

Persons not currently consuming alcohol include lifelong teetotalers and ex-drinkers. In most studies, ex-drinkers have significantly higher CAD rates than those who never drank. In the Tecumseh study, their risk was threefold compared with that for drinkers and teetotalers.[121] Wannamethee and Shaper point out that ex-drinkers have the highest prevalence of angina, electrocardiographic evidence of myocardial infarction, and self-reports of poor health; their standard CAD risk indicators are no more favorable than in other groups.[3]

Mild to Moderate Drinkers

In most cross-sectional studies, persons who drink alcohol but consume less than six drinks per day are less likely to have coronary artery disease than nondrinkers and heavier drinkers.[138,139] These findings were confirmed in prospective studies, including those from Hawaii,[140–142] Japan,[142] Massachusetts,[71] Puerto Rico,[143] London,[144] eastern Finland,[145] and Yugoslavia.[146] Study designs, however, often have not differentiated between ex-drinkers and those who never drank. The British Regional Heart Study made such a differentiation, examining men who did not have preexisting cardiovascular-related conditions. In that population, nondrinkers were at minimal risk, suggesting that the apparent benefits of consuming as many as five drinks per day may have been overemphasized.[147] In contrast, teetotalers free of clinical heart disease or other major recent illnesses who were part of the Kaiser-Permanente prepaid health plan had a higher rate of hospital admissions for coronary artery disease than ex-drinkers or current drinkers.[93]

Stroke

Within the past ten years, mortality from stroke has been almost halved in Japanese women and men and in men in the United States,[148] suggesting that the risk may be modifiable for both brain infarcts and hemorrhages. Although survival after a stroke has improved,[149] the stroke incidence has decreased more dramatically.[150] During the past 30 years, the relationship of alcohol abuse and stroke has been firmly established.[115]

The observed decreased regional cerebral blood flow in persons with both short- and long-term excessive alcohol intake[151] has been attributed to altered cerebral metabolism and to vasospasm of cerebrovascular smooth muscle. These effects, combined with those of alcohol-related disorders of blood pressure, coagulation, and cardiac rhythm discussed earlier, place heavy drinkers at a greater risk of stroke.[104]

Brain infarcts, which result primarily from underlying atherosclerotic cerebrovascular disease and from thromboembolism, are increased in incidence with heavy alcohol use.[152] Smoking, which frequently accompanies heavy alcohol use, has a detrimental effect on both atherosclerosis and clotting.

Hemorrhagic strokes may result from either subarachnoid hemorrhage due to the rupture of a circle of Willis aneurysm or from intraparenchymatous bleeding. The latter condition is usually associated with hypertensive changes in small penetrating arteries deep within the brain.[150] Because of its hemostatic effects, alcohol use increases the probability of hemorrhagic stroke.[140]

The relative proportions of infarct and hemorrhage in stroke cases vary with racial categories, often reflecting differences in risk factors. For example, hemorrhagic strokes constituted approximately 30% of strokes among Japanese-Hawaiian men,[153] but in the Framingham study, the percentage was only 15%.[150]

In addition to high blood pressure, hemostatic factors, and smoking, other possible causes of stroke more common in alcoholic patients include cardiac dysrhythmias and cardiomyopathy, as discussed earlier. In addition, alterations in cerebral blood flow and autoregulation occur with habitual alcohol intake.[104,154] These changes may result from the toxic effects of alcohol on cerebral metabolism and its direct vasospastic effects on cerebrovascular smooth muscle.[15]

The direct association of alcohol consumption and stroke has been noted in studies from many countries, including Japan,[155] Hawaii,[156,157] Yugoslavia,[146] the United Kingdom,[154] the US,[158] and Finland,[115] particularly in persons younger than 50.[105,158]

Investigators from the Honolulu Heart Study found that the stroke rate in heavy drinkers was elevated, regardless of blood pressure levels. They noted that consuming greater than 30 ml per day doubled the stroke risk.[157]

In the Yugoslavia Cardiovascular Disease Study, Kozararevic and colleagues compared heavier drinkers with those drinking only weekly; stroke rates were doubled in daily drinkers and tripled for those having two or more drinks per day.[146]

In a case-control study from Birmingham, England, light drinkers—10 to 90 grams per week—had only half the stroke rate of nondrinkers. In contrast, those men consuming 300 grams or more a week had a relative risk of 4.2 compared with nondrinkers.[154]

Hillbom noted the precipitation of both hemorrhagic and infarction strokes during intoxication rather than withdrawal in heavy drinkers by comparing stroke rates during different days of the week in those with and without alcohol ingestion within the 24 hours preceding the event. He and his coworkers also found that the incidence of alcohol-related strokes parallels the relative alcohol consumption in Finnish women and men, but the sex ratio in alcohol-unrelated strokes was nearer unity.[115]

Infectious Endocarditis

Buchbinder and Roberts found that of 59 patients with fatal active infective endocarditis, 14 (24%) had chronic alcoholism. Frequently the endocarditis was associated with pneumonitis or meningitis, an observation rarely mentioned in the medical literature since its initial description more than 100 years ago.[159] In a clinical and postmortem study, Snyder and co-workers found an increased concurrence of cirrhosis and bacterial endocarditis.[160] Of course, the prevalence of alcoholism in patients with any disease will depend on the population sampled, but the association between alcohol abuse and endocarditis appears to be both real and important.

Fetal Heart

Maternal heavy drinking can produce an alcohol embryopathy with characteristic defects in the atrial and ventricular septa.[161,162] In a prospective study of 1,016 children with congenital heart disease, 27 cases of embryopathies were defined. While 13 of the 27 were due to rubella infection, 10 resulted from maternal alcoholism.[163]

These findings add to those of many other studies of the fetal alcohol syndrome and have led most authorities to recommend that women abstain from drinking during pregnancy.[164]

Policy Implications

It appears that an average of one drink per day and the avoidance of binge drinking do not pose a significant additional risk for cardiovascular disease beyond abstinence in otherwise healthy adults.[77,82] The risks for alcoholic cardiomyopathy and an exacerbation of cardiac dysrhythmias, however, are clearly related to the amount of alcohol consumed. Coupled with the potential for alcohol abuse, these considerations preclude any recommendation for persons to begin drinking.

The risk of fetal cardiac abnormalities related to maternal drinking suggests a policy of abstinence for pregnant women.

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